Potential Risk and Protective Factors for In-hospital Mortality in Hyperacute Ischemic Stroke Patients

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In the era of thrombolytic therapy for hyperacute ischemic stroke, most investigators have focused their attention on the factors influencing mortality and functional outcomes in patients treated with thrombolysis, but very few have focused on these factors among patients not receiving thrombolysis. The aim of this study was to investigate the prognostic factors for mortality in all hyperacute stroke patients with or without thrombolysis. In 2005, we enrolled 101 ischemic stroke patients (43 females, 58 males; mean age, 68 years) who were transported to the emergency department (ED) within 4 hours of symptom onset. The overall in-hospital mortality rate was 17.8% (18/101). According to *t* test analysis, age ($p = 0.034$), time interval from neurologist consultation ($p < 0.0001$) and ED to ward admission ($p = 0.001$), Glasgow coma scale (GCS) ($p = 0.001$), National Institutes of Health Stroke Scale (NIHSS) ($p < 0.0001$) and the sum of major risk factors of cerebrovascular disease (CVD) ($p < 0.0001$) were significantly different between mortality and survivor groups. Further χ^2 test analysis revealed significant differences in the presenting consciousness disturbance ($p = 0.001$), place of attack ($p = 0.04$), and referral transportation ($p = 0.008$) between these groups. In conclusion, old age, delay between neurologist consultation and ward admission, severity of stroke, and multiple risk factors of CVD are significant risk factors for in-hospital mortality. Conversely, being free of initial consciousness disturbance, living in an urban area, and having direct transportation to a stroke center are protective factors in survivors. The concept of "brain attack" should be re-emphasized among ED physicians. The interconnection between stroke centers and emergency medical systems (EMS) should be more tightly built to promote timely management for hyperacute stroke care.

Key Words: hyperacute ischemic stroke, mortality, protective factor, risk factor, survival
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According to the literature, about 10–15% of stroke patients expired during hospitalization before clinical application of thrombolysis was available for acute ischemic stroke [1]. Since 1996, after the benefits of intravenous (IV) and intra-arterial (IA) thrombolytic therapy within the critical time windows of 3 and 6 hours, respectively, were recognized, hyperacute stroke has become an advanced concept and current issue. However, preliminary results suggested that thrombolytic therapy just improved functional outcome, but not mortality from all causes, and the relatively small percentage of patients receiving thrombolysis might have only a modest impact on hospital mortality [2].

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Several studies and recent Cochrane Collaboration meta-analyses have shown that more systematic stroke care improves efficiency, and reduces death and long-term institutionalization in patients admitted to stroke units [3]. In 2000, the Brain Attack Coalition (BAC), developed from a group of major professional organizations, published recommendations to establish minimal criteria for acute stroke centers with the goal of promoting timely administration of thrombolysis and improving stroke care [4]. Afterwards, many studies investigated the factors predictive of in-hospital mortality in acute stroke patients with thrombolysis [5–10].

Recently, two large national investigations found that in-hospital mortality from acute ischemic stroke was about 7.0% in academic medical centers (range, 2–12%) and 4.9% in community hospitals [11,12]. However, very few studies have evaluated the factors influencing mortality or functional outcomes in all hyperacute stroke patients with or without thrombolysis. As acute stroke team members in an academic hospital, we attempted to investigate the potential protective and risk factors for in-hospital mortality in all hyperacute ischemic stroke patients.

Materials and Methods

We set up a strict stroke code for patients with hyperacute stroke who were transported to our ED within 4 hours of the onset of stroke symptoms. Because IA thrombolysis requires much more preparation time than IV thrombolysis, 4 hours after stroke onset was the cut-off point in our study. For a period in 2005, consecutive patients activating the stroke code were registered prospectively [13].

Data included demographic features (sex, age, education level, residence), clinical information (initial presenting symptom and vital signs, time of symptom onset, hospital arrival, neurologist consultation, brain computed tomography (CT) performance, GCS, NIHSS, and laboratory data), and transportation mode (EMS, referral, other) were recorded. In addition, other variables including major risk factors of CVD, stroke territory, length of hospitalization and discharge status were collected from chart recording.

The major risk factors of CVD, including old age, history of stroke or transient ischemic attack (TIA), ischemic heart disease, atrial fibrillation, diabetic mellitus (DM), hypertension, hyperlipidemia and smoking, were noted for summation and well-documented [14]. Old age was defined as being older than 55 years and 50 years in females and males, respectively.

We categorized the stroke territory in all patients based on the neuroradiologist's report into five items: anterior cerebral artery (ACA), middle cerebral artery (MCA), internal carotid artery (ICA), posterior cerebral artery (PCA), and vertebral-basilar artery (VB). Only ICA territory was recorded under the situation when ipsilateral ACA and MCA were concomitantly involved.

Patients with hyperacute ischemic stroke were grouped into survivor and mortality cases according to discharge status. In-hospital mortality was defined as death from all causes on discharge from the acute hospital.

Influential factors between mortality and survivor groups that were presented as continuous variables were analyzed by the Student's t test. We used the χ^2 test to analyze the categorical variables for detecting risk and protective factors in enrolled patients. All statistical analyses were conducted with SPSS version 8.0 (SPSS Inc., Chicago, IL, USA), with statistical significance set at $p < 0.05$ (2-sided).

Results

We enrolled 101 patients with hyperacute ischemic stroke, including 43 females and 58 males with a mean age of 68 years (range, 36–91 years). The clinical characteristics of the enrolled patients are summarized in Table 1. Eighty-two patients suffered an attack in an urban area and 19 patients suffered an attack in a rural area. The proportions of patients transported to the ED via EMS and following referrals from other hospitals were 32.7% (33/101) and 15.8% (16/101) respectively. Only 12 (11.9%) patients received IV tissue plasminogen activator (t-PA) or IA urokinase thrombolytic therapy, and two patients (both post-IV t-PA) died during acute hospitalization. The number of cases of in-hospital all-cause mortality in hyperacute ischemic stroke patients was 18 (17.8%).

The relative proportions of involvement of each involved vascular territory in ischemic stroke were as follows: ACA 2.83% (3/106), MCA 73.58% (78/106), ICA 5.66% (6/106), PCA 4.71% (5/106), and VB system 13.2% (14/106). There were five patients with two distinctive territories. Overall, 84 (83.2%) and 17 (16.8%)

Table 1. Demographic and clinical characteristics of enrolled patients*

Age (yr)	68.2 ± 11.6
Sex	
Female	43 (42.6)
Male	58 (57.4)
Education (yr)	
Illiterate	25 (24.8)
≤ 9	51 (50.4)
> 9	25 (24.8)
Thrombolytic therapy, IV/IA	12, 10/2 (11.9)
Mortality	18 (17.8)
Thrombolysis (both IV t-PA)	2 (2.0)
Non-thrombolysis	16 (15.8)
GCS	12.8 ± 3.3
NIHSS	11.8 ± 9.5
Distribution of stroke territory	
ACA	3 (2.8)
MCA	78 (73.6)
ICA	6 (5.7)
PCA	5 (4.7)
VB	14 (13.2)
Sum of risk factors†	
≤ 2	40 (39.6)
3	28 (27.7)
4	20 (19.8)
≥ 5	13 (12.9)
Place of attack	
Urban	82 (81.2)
Rural	19 (18.8)
Mode of transportation	
EMS	33 (32.7)
Referral	16 (15.8)
Other	52 (51.5)

*Data presented as mean ± standard deviation or *n* (%); †risk factors for ischemic stroke included old age, history of stroke or transient ischemic attack, ischemic heart disease, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, smoking. GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale; EMS = emergency medical system.

patients were respectively categorized as showing anterior- and posterior-circulation involvement.

We also evaluated differences in demography, clinical characteristics and influential factors between mortality and survivor groups (Tables 2 and 3). The mean age was 73.2 ± 10.2 years in mortality cases and 67.1 ± 11.6 years in survivor cases ($p = 0.034$). The mean time intervals from ED presentation to neurologist consultation and ward admission were 132 ± 96.7 and 233.2 ± 116.3 minutes, respectively, in the mortality group, and 10.2 ± 8.6 and 112.3 ± 74.1 minutes, respectively, in the survivor group ($p < 0.0001$ and $p = 0.01$). In the mortality group, the mean GCS and NIHSS scores were 9.6 ± 4.2 and 22.5 ± 8.7, respectively; in the survivor group, these were 13.5 ± 2.6 and 9.5 ± 8.1 ($p = 0.001$ and $p < 0.0001$) respectively. Furthermore, the mean sum of major risk factors in mortality cases was 3.9 ± 1.0 and that in survivor cases 2.8 ± 1.2 ($p < 0.0001$) (Table 2). According to *t* tests, age, time interval of ED presentation to a neurologist and ward admission, GCS, NIHSS and the sum of major risk factors were significantly different ($p < 0.05$) between mortality and survivor groups.

From χ^2 analysis, further significant differences were revealed between mortality and survivor groups in initial consciousness disturbance ($p = 0.001$), place of attack ($p = 0.04$), and referral transportation ($p = 0.008$) (Table 3). In the survivor group, 85.5% (71/83) of patients had initial symptom onset in an urban area. The mortality rates in rural and urban areas were 36.8% (7/19) and 13.4% (11/82), respectively. Most of the patients in the survival group, 89.2% (74/83), were not transported via referral hospital, and patients with referral transportation had mortality rates of 43.8% (7/16) versus 12.9% (11/85) in those without referral transportation. Only 14 patients (16.9%) in the survivor group had an initial consciousness disturbance, compared with 69 patients (83.1%) without consciousness change. The patients that did not present with consciousness disturbance had a survival rate of 89.6% (69/77). The mortality rate was 41.7% (10/24) in patients with consciousness disturbance.

Discussion

The in-hospital mortality and functional outcome in acute stroke vary according to different stroke type, severity and enrolled criteria in different dimensions. In Steiner and Brainin's investigation of data from the Austrian Stroke Registry for acute stroke units (which enrolled patients within 24 hours after symptom onset), the overall stroke-unit mortality was about 6.8% [15]. In another study in the USA, the in-hospital mortality rate of acute ischemic stroke patients was about 2–12% in academic hospitals, without clear inclusion criteria for time [11]. According to previous thrombolysis trials, the 3-monthly mortality rates in

Table 2. Influential factors for in-hospital mortality in hyperacute ischemic stroke

Variable	Mortality ($n=18$)	Survivor ($n=83$)	p*
Age (yr)	73.2±10.2	67.1±11.6	0.034
Time interval (min)			
Onset to ED	116.6±78.6	93.0±59.7	0.270
ED to neurologist	132.7±96.8	10.2±8.6	<0.0001
ED to CT	31.1±23.5	22.1±12.5	0.238
ED to ward	233.2±116.3	112.3±74.1	0.001
Initial BP (mmHg)			
SBP	165.0±33.4	157.9±32.2	0.421
DBP	88.3±23.1	90.0±19.9	0.765
Severity			
GCS	9.6±4.2	13.5±2.6	0.001
NIHSS	22.5±8.7	9.5±8.1	<0.0001
Blood sugar on admission (mg/dL)	159.5±58.6	138.3±53.4	0.183
Sum of risk factors	3.9±1.0	2.8±1.2	<0.0001
Hospitalization (d)	9.3±7.0	11.6±8.5	0.239

*t test. GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale.

placebo groups *vs*. treatment groups were 21% versus 17% in the IV t-PA trial (≤ 3 hours), and about 3.5–27% versus 5.3–25% in the IA thrombolysis trial (≤ 6 hours) [2,16,17]. In our study, the overall in-hospital mortality from all causes in hyperacute ischemic stroke patients (≤ 4 hours) was 17.8% (18/101), suggesting that there are still many factors influencing the mortality rate in our series.

In order to predict mortality and outcome in acute stroke patients, various measures have been established according to stroke subtype etiology and severity [18,19]. In general, our results in Table 2 are compatible with those of many previous studies, showing that the mortality group has advanced age [20], higher GCS and NIHSS with serious stroke severity [21–23], and more CVD risk factors [18,24].

In this study, there was an obvious time delay in neurologist consultation at the ED (132.7±96.8 *vs.* 10.2±8.6 minutes), as well as in transferal to the neurological ward (233.2±116.3 *vs.* 112.3±74.1 minutes) between these two groups. The reasonable explanation for this is that the ED physician spent more time managing the initial unstable vital signs and in making the differential diagnosis in severe stroke patients.

Evidently, those patients free of consciousness disturbance had significantly higher survival rates than those presenting with consciousness disturbance (69/77, 89.6% *vs.* 14/24, 58.3%), because they were considered to have milder stroke severity and less complicated illness. In the mortality group, there was a high rate of initial consciousness disturbance (10/18, 55.6%). These patients usually showed greater clinical severity, and were supposed to undergo many laboratory, image exams and multidisciplinary consultations at the ED. These results are also supported by some prior literature [18,25,26]. Besides, we noted that the patients with initial speech disorder (including dysphasia or dysarthria) had a lower risk for in-hospital mortality (2/40, 5%). We thought this might be due to under-reporting of the concomitant speech problem in unconscious patients, and the number of cases with a speech disorder in the mortality group might be under-estimated. Another possibility is a lower stroke severity in those patients presenting only with dysphasia or dysarthria.

Patients living in urban areas had higher survival rates than those living in rural areas (71/82, 86.6% *vs.* 12/19, 63.2%). It is understandable that there are more available medical facilities and more convenient transportation in urban areas. Patients visiting the ED via direct transportation had markedly increased survival rates compared with patients with arriving following referral (74/85, 87.1% *vs.* 9/16, 56.3%). We presumed that these patients might have worse clinical manifestations, and needed further transfer to a medical center for better management.

Table 3. Risk and protective factors between mortality and survivor groups

Variable	Mortality, *n* (%)	Survivor, *n* (%)	*p**
Age (yr)			0.116
≥65	14 (77.8)	47 (56.6)	
<65	4 (22.2)	36 (43.4)	
Sex			0.601
Female	9 (50)	34 (41.0)	
Male	9 (50)	49 (59.0)	
Education			0.140
Literate	11 (61.1)	65 (78.3)	
Illiterate	7 (38.9)	18 (21.7)	
CVD PH			0.594
Yes	8 (44.4)	30 (36.1)	
No	10 (55.6)	53 (63.9)	
Initial symptoms			
Consciousness disturbance			0.001
Yes	10 (55.6)	14 (16.9)	
No	8 (44.4)	69 (83.1)	
Weakness			0.158
Yes	10 (55.6)	61 (73.5)	
No	8 (44.4)	22 (26.5)	
Speech disorder			0.007
Yes	2 (11.1)	38 (45.8)	
No	16 (88.9)	45 (54.2)	
Territory			0.479
Anterior circulation	14 (77.8)	70 (84.3)	
Posterior circulation	4 (22.2)	13 (15.7)	
Place of attack			0.040
Urban	11 (61.1)	71 (85.5)	
Rural	7 (38.9)	12 (14.5)	
Referral			0.008
Yes	7 (38.9)	9 (10.8)	
No	11 (61.1)	74 (89.2)	

*χ^2 test. CVD PH = past history of cerebrovascular disease and cardiovascular disease.

In our series, there were still some influential factors, such as initial systolic and diastolic blood pressure, blood sugar and days of hospitalization; combining these influential factors, age above 65, education level, and presentation of weakness, and stroke territory showed no significant difference. These results are not compatible with those of previous studies. The reason for this might be related to small case numbers in these variables. In order to solve this limitation of our study, we expect that the Taiwan Stroke Registry for acute stroke enrollment could answer the above questions.

In conclusion, old age, delays in consultation by the attending neurologist and ward admission, severity of stroke (initial GCS and NIHSS), and multiple CVD risk factors are significant risk factors for in-hospital mortality. Conversely, being free of initial consciousness disturbance at ED presentation, living in an urban area, and having direct transportation to a stroke center are strongly protective factors for survival cases. The concept of "brain attack" should be re-emphasized, particularly among ED physicians either in academic or community hospitals. The interconnection between stroke centers and local EMS should be more tightly

integrated to promote timely management in hyperacute stroke care.

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References

1. Brown RD, Whisnant JP, Sicks JD, et al. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373–80.
2. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581–7.
3. Stroke Unit Trialists' Collaboration. Organized inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2000;2:CD000197.
4. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. *JAMA* 2000;283:3102–9.
5. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA* 2000;283:1151–8.
6. Heuschmann PU, Berger K, Misselwitz B, et al. Frequency of thrombolytic therapy in patients with acute ischemic stroke and the risk of in-hospital mortality: the German Stroke Registers Study Group. *Stroke* 2003;34: 1106–13.
7. Heuschmann PU, Kolominsky-Rabas PL, Roether J, et al. Predictors of in-hospital mortality in patients with acute ischemic stroke treated with thrombolytic therapy. *JAMA* 2004;292:1831–8.
8. Bateman BT, Schumacher HC, Boden-Albala B, et al. Factors associated with in-hospital mortality after administration of thrombolysis in acute ischemic stroke patients: an analysis of the nationwide inpatient sample 1999 to 2002. *Stroke* 2006;37:440–6.
9. Dubinsky R, Lai SM. Mortality of stroke patients treated with thrombolysis: analysis of nationwide inpatient sample. *Neurology* 2006;66:1742–4.
10. Elkind MS, Prabhakaran S, Pittman J, et al. Sex as a predictor of outcomes in patients treated with thrombolysis for acute stroke. *Neurology* 2007;68:842–8.
11. Leslie AG, Johnston SC. Characteristics of academic medical centers and ischemic stroke outcomes. *Stroke* 2001;32:2137–42.
12. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German Stroke Registers Study Group. *Arch Intern Med* 2004;164: 1761–8.
13. Huang Poyin, Chen CH, Liu CK, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke. *Cerebrovasc Dis* 2006;22:423–8.
14. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham study. *Stroke* 1991;22:312–8.
15. Steiner MM, Brainin M. The quality of acute stroke units on a nation-wide level: the Austrian Stroke Registry for acute stroke units. *European Journal of Neurology* 2003;10:353–60.
16. Anthony F, Randall H, Lawrence W, et al. Intra-arterial prourokinase for acute ischemic stroke the PROACT II study: a randomized controlled trial. *JAMA* 1999;282: 2003–11.
17. Akira O, Etsuro M, Kazuo M, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke* 2007;38:2633–9.
18. Sacco RL. Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology* 1997;40:39–44.
19. Henon H, Durieu I, Lebert F, et al. Influence of prestroke dementia on early and delayed mortality in stroke patients. *J Neurol* 2003;250:10–6.
20. Weimar C, Ziegler A, Konig IR, et al. Predicting functional outcome and survival after acute ischemic stroke. *J Neurol* 2002;249:888–95.
21. Frankel MR, Morgenstern LB, Kwiatkowski T, et al. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology* 2000; 55:952–9.
22. Handschu R, Haslbeck M, Hartmann A, et al. Mortality prediction in critical care for acute stroke: severity of illness-score or coma-scale. *J Neurol* 2005;252:1249–54.
23. Rordorf G, Koroshetz W, Efird JT, et al. Predictors of mortality in stroke patients admitted to an intensive care unit. *Crit Care Med* 2000;28:1301–5.
24. Wong KS. Risk factors for early death in acute ischemic stroke and intracerebral hemorrhage: a prospective hospital-based study in Asia. *Stroke* 1999;30:2326–30.
25. Sumer MM, Ozdemir I, Tascilar N. Predictors of outcome after acute ischemic stroke. *Acta Neurologica Scandinavica* 2003;107:276–80.
26. Holloway RG, Benesch CG, Burgin WS, et al. Prognosis and decision making in severe stroke. *JAMA* 2005;294: 725–33.

超急性缺血性腦中風病患住院中死亡之潛在危險因子及保護因子

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在血栓溶解療法應用於超急性缺血性腦中風的時代開啟之後，大部分的研究都集中在探討血栓溶解療法之後的死亡率及病情轉變，很少同時討論到未經血栓溶解療法病人的病況。我們的研究目的就是要探討所有超急性缺血性腦中風病人住院中死亡的影響因子。於 2005 年這一年內，我們收錄了在中風症狀發作後四小時內的超急性缺血性腦中風病患，並分析他們的潛在預後因子。我們共收錄了 101 位病人，43 位女性及 58 位男性，平均年齡為 68 歲。整體住院中死亡率為 17.8% (18/101)。根據 *t* test 統計分析，年齡 ($p = 0.034$)、急診到會診神經科醫師 ($p < 0.0001$) 和急診到病房住院的時間間距 ($p = 0.001$)、GCS ($p = 0.001$)、NIHSS ($p < 0.0001$) 及主要中風危險因子總數 ($p < 0.0001$)，在死亡及存活組間存在顯著的差異。此外，這兩組於初始期意識障礙 ($p = 0.001$)、中風發生地 ($p = 0.04$) 及轉院運送 ($p = 0.008$) 有著顯著的不同。總結來說，年長者、延遲照會神經醫師及住院、中風嚴重度及多種中風危險因子與病患死亡有顯著的相關。相對的，未以意識模糊為初始表現者、居住在城市及直接運送病患到腦中風醫療中心，可視為存活的保護因子。我們強調“腦發作”的觀念應該於急診醫師間再廣為推廣。此外，腦中風醫療中心與緊急醫療系統應該建構成更緊密的聯絡網，促進超急性腦中風及時處置的成效及照護品質。

關鍵詞：超急性缺血性腦中風，死亡率，保護因子，危險因子，存活者

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